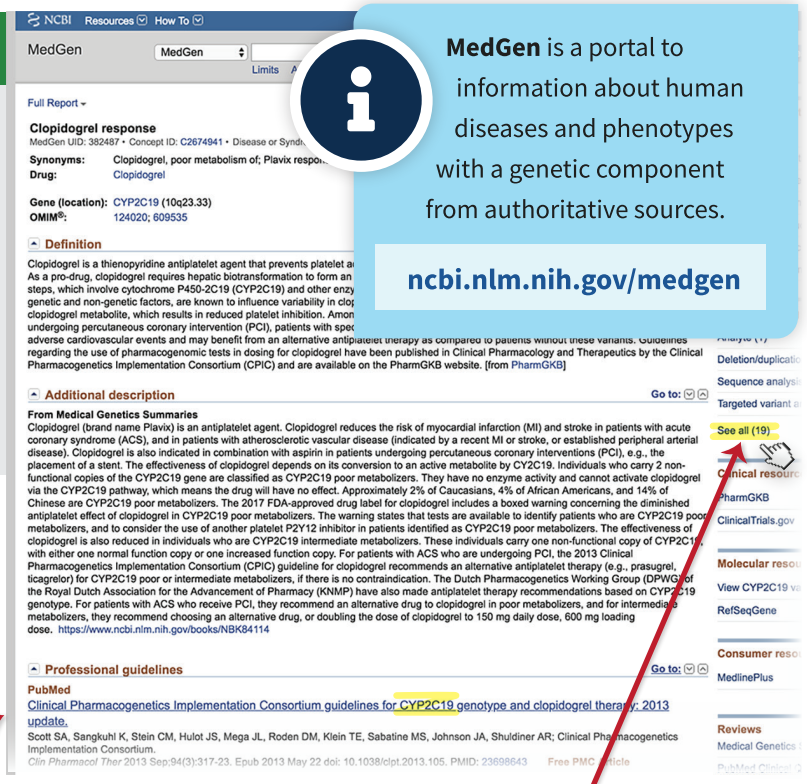
NCBI Pharmacogenetics Resources for Clinical Care

Step-by-step tutorial

ncbi.nlm.nih.gov/medgen

Case Study

You diagnose a patient with Acute Coronary Syndrome and schedule an angioplasty. You explain to the patient that she will need to take clopidogrel, also known as Plavix, for at least 3-6 months to prevent a heart attack. The patient tells you that her father died of a heart attack while taking clopidogrel. So, you decide to look into the pharmacogenetics of clopidogrel response to see if a change in the prescription is indicated.



MedGen is a portal to information about human diseases and phenotypes with a genetic component from authoritative sources.

ncbi.nlm.nih.gov/medgen

Learn about optimizing an initial dose, avoiding side effects and the drug therapy recomendations based on genotype in MedGen

Step 1 Look up Clopidogrel response in MedGen

The role of *CYP2C19* clopidogrel metabolism is summarized here. You notice therapeutic recommendations by the FDA and professional societies based on a patient's *CYP2C19* genotype.

Step 2 Go to the NIH Genetic Testing Registry (GTR)

Click on the See all (19) link to go to a list of available genetic tests for clopidogrel response registered in GTR.

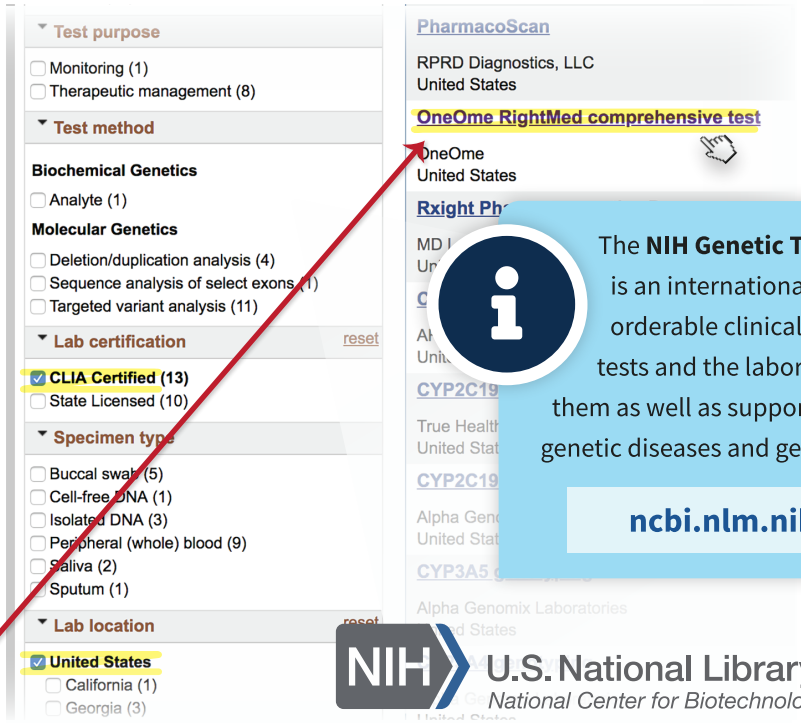
Select an appropriate genetic test to order for your patient in the NIH GTR

Step 3 Narrow your search

Check the boxes on the left to filter the list of tests based on your desired parameters. For example: you want the specimen type to be a buccal swab from a lab that is CLIA Certified in the United States.

Step 4 Learn about a specific test

Select a test from the list to see more details: click on OneOme RightMed comprehensive test.

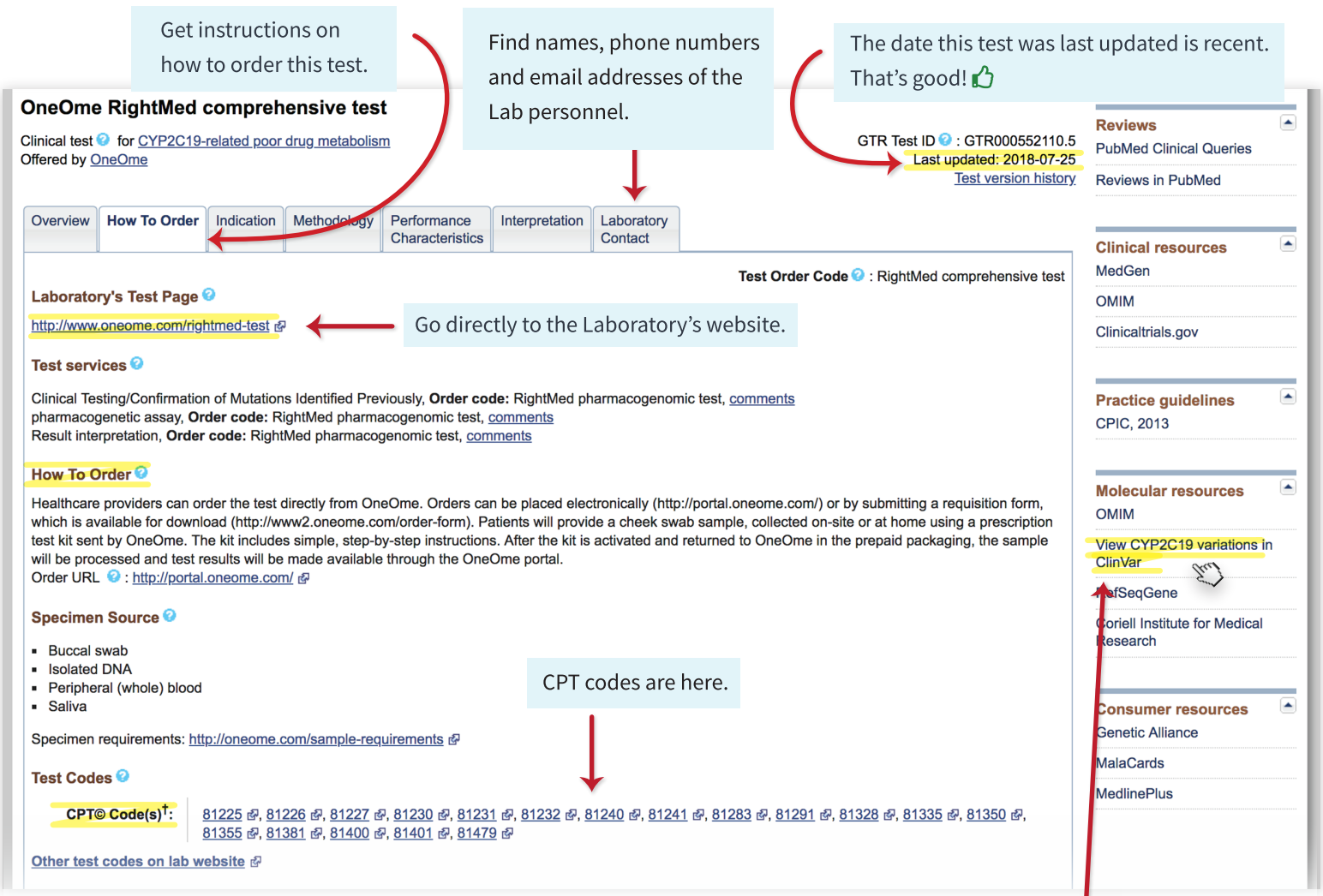


The **NIH Genetic Testing Registry** (GTR) is an international database of orderable clinical and research genetic tests and the laboratories that provide them as well as supporting resources about genetic diseases and genes.

ncbi.nlm.nih.gov/gtr

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

Step 5 Browse the test detail page to learn about its clinical and analytical validity, clinical utility and how to order it



Step 6 See what information is currently known for this gene's variants in this gene in ClinVar.

Click on View *CYP2C19* variations in ClinVar to see a list of reports of the relationships among variants in the *CYP2C19* gene and phenotypes, with supporting data, as provided by submitters like testing laboratories and researchers.

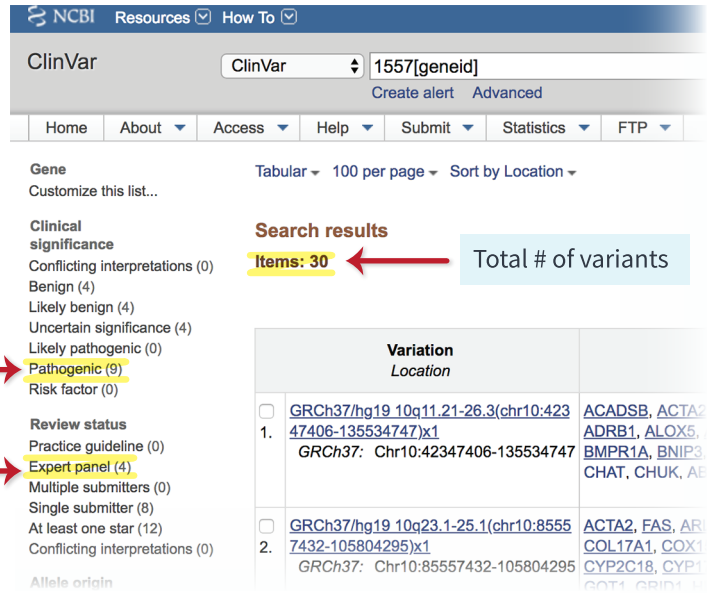
Use ClinVar to help interpret the genetic test result

ClinVar is a database that archives information about human genetic variations and their relationship to human health, with supporting evidence.

ncbi.nlm.nih.gov/clinvar

Step 7 Focus on the most significant variants in ClinVar

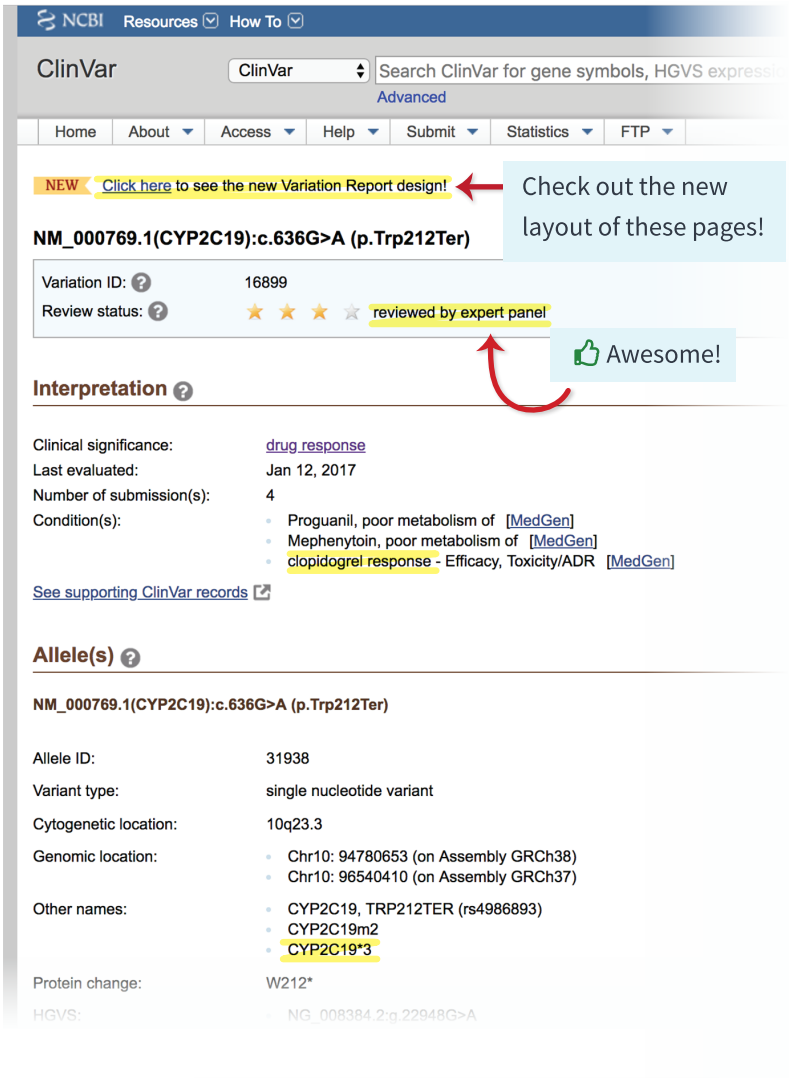
As you explore the impact of *CYP2C19* variants, focus on the most clinically significant, such as those flagged as pathogenic and those that have been reviewed by an expert panel.



The genetic test results arrive! It is reported that the patient is homozygous with two alleles of *CYP2C19* p.Trp212Ter.

Step 8 Search ClinVar with *CYP2C19* p.Ter212Ter

The clinical significance of this variant is that it influences *clopidogrel response*. It has been *reviewed by expert panel*. Other information is provided here including allele frequency and Other names such as CYP2C19*3, which is a common clinical nomenclature.



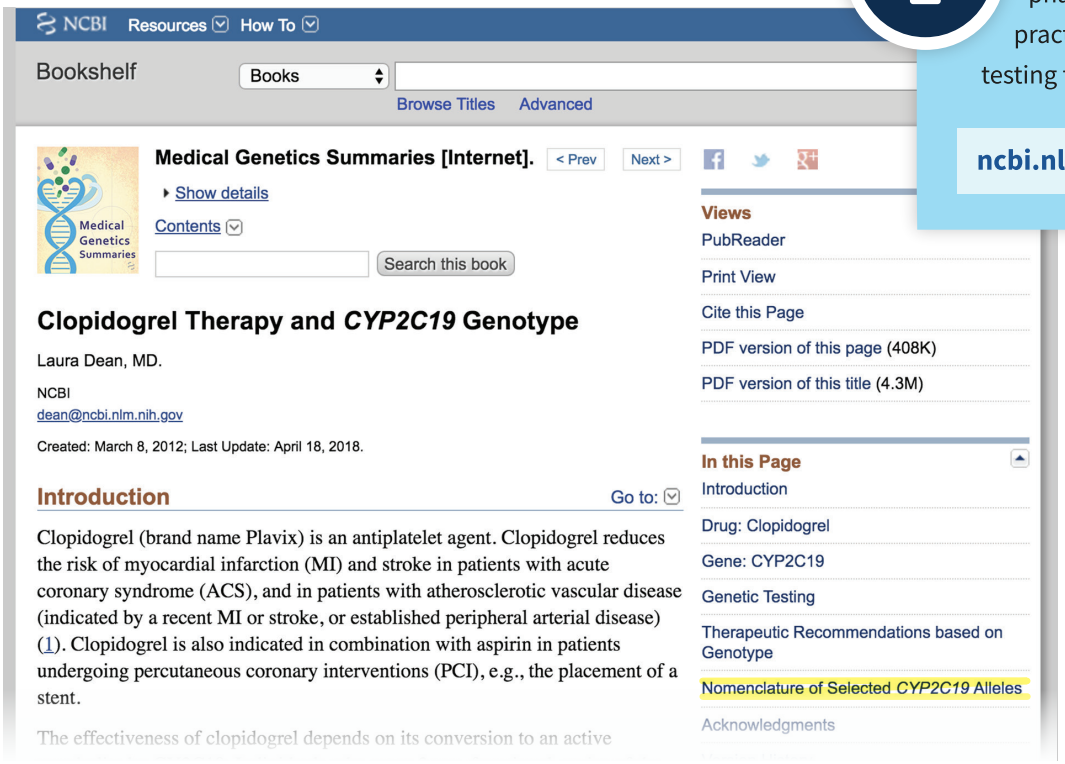
Find actionable information in Medical Genetics Summaries

Step 9 Read more about it in Medical Genetics Summaries.

Learn more about clopidogrel, *CYP2C19* and its role in the drug's metabolism. Go back to the **MedGen** record for *Clopidogrel response* (**ncbi.nlm.nih.gov/medgen/382487**). From here, click on the Medical Genetics Summaries link under **Reviews** on the right sidebar.

Medical Genetics Summaries is a collection of articles which synthesize pharmacogenetic evidence to provide practical information about genetic testing to guide drug therapy.

ncbi.nlm.nih.gov/books/NBK84114/



Step 10 Navigate the page to the content of interest

The table of contents enables you to go directly to the *Nomenclature of Selected CYP2C19 Alleles* section.

Step 11 Allele nomenclature standardization

The table Nomenclature of Selected *CYP2C19* Alleles translates the terms used for variants, from the common star allele (*3) to the HGVS expression (NM_000769.1:c.636G>A), and provides links to the *CYP2C19*3* records in dbSNP (rs4986893) and ClinVar (ID 16899).

Nomenclature of Selected *CYP2C19* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Note: the normal "wild type" allele is *CYP2C19*1* and is reported when no variant is detected.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (60).

Table 2.

CPIC (2013) Antiplatelet Therapy Recommendations based on *CYP2C19* Status when considering Clopidogrel for ACS/PCI Patients.

Phenotype	Examples of diplotypes	Implications for clopidogrel	Therapeutic recommendations for clopidogrel in ACS/PCI[a]
Ultrarapid metabolizer	**17/*17*	Increased platelet inhibition; decreased residual platelet aggregation[b]	Dose recommended by drugs label
Rapid metabolizer	**1/*17*		
Normal metabolizer	**1/*1*	Normal platelet inhibition; normal residual platelet aggregation	Dose recommended by drug label
Intermediate metabolizer	**1/*2* **1/*3* **2/*17*	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor
Poor metabolizer	**2/*2* **2/*3* **3/*3*	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor

[a] The strength of therapeutic recommendations is "moderate" for intermediate metabolizers and "strong" for all other metabolizers. See Supplementary Materials and Methods (Strength of Therapeutic Recommendations) online.
[b] The *CYP2C19*17* allele may be associated with increased bleeding risks, see (4).

Step 12 Clopidogrel dosing recommendations from authoritative sources

All available therapeutic recommendations from medical or professional societies such as CPIC and DPWG are summarized here, with full-text versions cited and linked.

In this section is a summary of the **2017 Statement from the US Food and Drug Administration** (FDA) among others. At the end of the summary, there is a link to review the complete therapeutic recommendations. This takes you to DailyMed where you will find a warning message.

2017 Statement from the US Food and Drug Administration (FDA)

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of clopidogrel tablets results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel tablets at [illegible] in both positive effects (reduction in the risk of serious cardiovascular events) and negative effects (increase in the risk of bleeding).

Please review the complete therapeutic recommendations that are located here: (1)

Conclusion

The patient's genotype indicates that she is a poor metabolizer for clopidogrel. Based on the available evidence and therapeutic recommendations, you decide to use an alternative antiplatelet drug and change your prescription to prasugrel, which is not metabolized by *CYP2C19*.

References

MedGen ncbi.nlm.nih.gov/medgen

GTR ncbi.nlm.nih.gov/gtr

ClinVar ncbi.nlm.nih.gov/clinvar

Medical Genetics Summaries ncbi.nlm.nih.gov/books/NBK84114/

Need help? Email us at medgen_help@ncbi.nlm.nih.gov.

YouTube **Watch a video of this tutorial.** https://youtu.be/HOixfcWeDxU

NIH U.S. National Library of Medicine
National Center for Biotechnology Information